Which Drugs Benefit Diabetic Patients for Secondary Prevention of Myocardial Infarction?

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Diabetic patients have increased mortality following myocardial infarction. We review the evidence for benefit in diabetic patients, of the major drug groups used as secondary prevention. *Beta blockers*: meta-analyses suggest a reduction in mortality of 35 % with beta blockers. Diabetic patients should receive beta blockers post myocardial infarction. In many patients, the benefits of beta blockers will outweigh relative contraindications. *Aspirin*: meta-analyses of antiplatelet therapy in high-risk subjects have shown substantial benefits. Aspirin should be prescribed for secondary prevention. *Lipid lowering with statins:* subgroup analyses of the major secondary prevention trials show substantial benefits across a wide range of baseline cholesterol and LDL levels. These drugs should be prescribed as *secondary* prevention to patients with diabetes whose total cholesterol is $> 4.0\ mmol^{-1}$. *Angiotensin converting enzyme inhibitors* (ACEIs): the few subgroup analyses that exist from ACEI trials suggest that diabetic and non-diabetic patients derive similar benefits. Diabetic subjects who have systolic dysfunction after myocardial infarction should receive ACEIs. *Treatment combination:* data exist to suggest that most of these drugs produce benefit independently. *Conclusion:* diabetic patients benefit from secondary prevention with drug treatment as much as, or more than, non-diabetic patients. © 1998 John Wiley & Sons, Ltd.

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Introduction

The St Vincent Declaration has called for concerted action on cardiovascular disease,[1] recognizing that this is the principle cause of morbidity and premature mortality in diabetic patients. Indeed, cardiovascular disease accounts for almost 80 % of all 'diabetic' deaths,[2] a large proportion of which are due to myocardial infarction.[3] It has long been recognized that diabetic patients have a higher risk of suffering an acute myocardial infarction compared with the non-diabetic population.[4] In addition, acute myocardial infarction has a greater than two-fold higher mortality rate in the short term,[5,6] as well as a reduced long-term survival[7–9] probably for many reasons.[10] Diabetic patients suffer more complications following myocardial infarction,[11] especially heart failure[12] and recurrent myocardial infarction.[13,14]

The effectiveness of pharmacotherapy after myocardial infarction in general populations has been meticulously studied in the context of large randomized controlled studies. Few, if any, studies have been carried out exclusively in the diabetic population and many studies have excluded diabetic patients. Important questions thus remain about the optimal treatment of diabetic patients after myocardial infarction. Current diabetic management strategies are often based on the premise that drug treatments that benefit non-diabetic subjects produce parallel benefit in people with diabetes.[15] This review aims to determine whether this is a legitimate approach. Specifically, we examine the evidence that the four major drug groups with proven benefits for patients in terms of secondary prevention, beta blockers, aspirin, lipid lowering agents, and angiotensin converting enzyme (ACE) inhibitors, are beneficial in diabetic patients. We also examine the possible role of other drugs in secondary prevention.

Secondary Prevention Trials Post Myocardial Infarction

Beta Blockers

Meta-analyses of data from 29 trials of beta blockers given to 28 970 patients during myocardial infarction

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and 26 trials where beta blockers were started in 24 298 subjects after the acute event have shown the benefit of both approaches, the overall mortality risk reduction of 13% and 23%, respectively.[16] Only six randomized studies have reported results stratified for diabetes (Table 1). Of these, three were studies of beta blockers given during myocardial infarction, the largest of which was the First International Study of Infarct Survival (ISIS 1).[17] This study included 958 diabetic patients out of a total of 16 029 patients, who within 12 h (mean 5 h) of the onset of symptoms were randomized to receive intravenous atenolol or placebo, followed by 7 days of oral therapy. Twenty-nine deaths occurred in the 463 diabetic subjects who received beta blocker, versus 40 of the 495 who received placebo (NS). Similar non-significant trends were seen in the Metoprolol In Acute Myocardial Infarction (MIAMI) study (413 diabetic subjects)[18] and the Goteborg study (120 diabetic subjects).[18]

Three studies examined beta blockers started 5–28 days after a myocardial infarction and follow-up was 1 or more years. The largest study was the Beta blocker Heart Attack Trial (BHAT);[19] however out of the 3837 subjects randomized, only 465 had diabetes. Twenty-two deaths occurred in 236 beta blocker treated diabetic subjects compared to 33 out of 224 who received placebo (NS). Similar but significant results were seen in the Norwegian Timolol Multicenter Study, with a reduction in deaths from 14 in the placebo group to 6 in the treatment group ($p < 0.05$).[20] Only one small study of pindolol showed a negative trend but this included only 36 diabetic patients.[21] One observational study has also been reported.[22] This followed up 281 diabetic subjects who survived myocardial infarction. Subjects taking beta blockers had a 1 year mortality of 10% compared with 23% in those not taking these drugs. However, this study is confounded as certain subjects at high risk of death, such as subjects with airways disease, may not be given beta blockers.

Wilhelmsen has carried out a meta-analysis of the six randomized studies of beta-blocker treatment in diabetic subjects (Lars Wilhelmsen, personal communication). He found a 35% risk reduction in favour of beta-blockade ($p = 0.0014$). Similar pooling of data have suggested a 37% reduction in mortality in diabetic subjects given beta blockers during myocardial infarction versus a 13% reduction in non-diabetic.[22,23] In studies that started beta blockers after myocardial infarction, pooled results have estimated a staggering 48 % reduction in mortality in diabetic subjects versus 33 % in subjects without diabetes, the figures for reinfarction being 55 % versus 21 %.[24] Overall, the evidence is compelling that beta blockers reduce reinfarction and sudden death in diabetic patients at least as effectively and probably to a greater extent than in non-diabetic patients.

Barriers to Beta Blocker Prescribing Post Myocardial Infarction

Studies of beta blocker use have shown that there appears to be a reluctance to prescribe beta blockers post myocardial infarction even to subjects without diabetes.[25–29] Most cardiologists believe that beta blockers improve survival[30] and beta blocker under-use is a growing concern.[31] Barriers to their use may include mistaken beliefs that these agents are harmful or less beneficial in diabetic patients. Since the benefits of beta blockade appear greater in diabetes, their use should be considered in all patients except those with absolute contraindications.[32] Deterioration in glycaemic control or blunted counterregulatory responses to hypoglycaemia are seldom clinically important problems, especially with cardioselective beta blockers.[33] Critical limb ischaemia is an absolute contraindication, but peripheral vascular disease with intermittent claudication is not.[34] Asthma is an absolute contraindication but a proportion of subjects with chronic obstructive airways disease may tolerate beta blockade. A trial of beta blocker therapy might be a reasonable strategy in such patients, on the basis that treatment can be stopped if symptoms deteriorate significantly. Perhaps celiprolol, which has β_2 agonist properties, might be the drug of choice in such patients. Heart failure is often cited as a

Table 1. Results of main beta blocker trials which included patients with diabetes, expressed as changes in total mortality

Study	Follow-up	Subjects	Diabetics	Mortality (%) Treatment	Mortality (%) Placebo	RRR[b]	NNT[c]
During Myocardial Infarction							
ISIS1	7 days	16027	958	6.5	8.1	20%	62
MIAMI	15 days	5778	413	5.7	11.3	49%	18
Goteborg	3 months	1395	120	7.5	17.9	58%	10
After Myocardial Infarction							
Norwegian	17 months	1884	99	11.3	30.5	63%	5
BHAT	25 months	3837	465	9.3	14.4	35%	20
Kjekshus[a]	12 months	1716	268	10.2	23.4	56%	8
Australian	48 months	529	36	42.9	22.7	–89%	–

a Observational study not a randomised trial.
b RRR = relative risk reduction.
c NNT = number needed to treat to prevent death in one.

contraindication to beta blockade post myocardial infarction but this view has been challenged by the publication of trials that demonstrate improved morbidity and mortality of beta blockade with carvedilol in heart failure,[35] even in severe heart failure.[36] In fact, the Beta-Blocker Heart Attack Trial[19] included 710 subjects with mild congestive heart failure. In this subgroup, propranolol reduced mortality by 27% compared to placebo,[37] so mild to moderate heart failure does not seem to be a contraindication to treatment. Studies with several other beta blockers have suggested that this benefit may be a class effect.[38] Furthermore, recent data from the Survival and Ventricular Enlargement Study (SAVE)[39] provides further evidence that beta blockers are beneficial in subjects who suffer a myocardial infarction complicated by heart failure as beta blockade reduced cardiovascular mortality by 30 % and recurrent heart failure by 21 %. Finally, worries about reduced quality of life[40] or dyslipidaemia[41] have been largely unsubstantiated.

Beta Blockers: the Verdict

Although based on subgroup analyses, the evidence for benefit is strongly in favour of beta blockade both acutely and in the long term. As it is unlikely that further evidence will become available, all diabetic patients should receive intravenous beta blockers acutely, followed by oral therapy post myocardial infarction. Since the benefits appear substantial, subjects with relative contraindications such as mild peripheral vascular disease and fixed airways obstruction should at least receive a trial of therapy. Beta blockers appear particularly beneficial in patients with left ventricular dysfunction.

Aspirin

No trials of aspirin after myocardial infarction have been conducted exclusively in diabetic patients. The effect of aspirin on *primary* prevention of myocardial infarction has been studied as a subgroup analysis of the Early Treatment Diabetic Retinopathy Study.[42] This demonstrated a non-significant reduction in fatal and non-fatal myocardial infarction (relative risk 0.83 99 % CI 0.66–1.04), but no reduction in mortality (relative risk 0.91 99 % CI 0.75–1.11) in those randomized to receive aspirin 325 mg day^{-1}. The Antiplatelet Trialists Collaboration have published the most comprehensive meta-analysis of the benefits of antiplatelet agents (mainly aspirin) in non-diabetic and diabetic patients.[43] The benefits of aspirin for secondary prevention of myocardial infarction are not in doubt. Overall aspirin and antiplatelet agents reduce cardiovascular morbidity by 25% and mortality by 15 %. In the non-diabetic patient this results in the avoidance of 6 non-fatal strokes, 18 non-fatal reinfarctions, 13 vascular deaths, and 12 any cause deaths if 1000 post myocardial infarction patients are treated for 27 months. The only direct comparison that can be made between subjects with and without diabetes is a meta-analysis of 29 'high risk' trials.[43] In this analysis, aspirin/antiplatelet therapy produced similar proportional reductions in mortality in diabetic and non-diabetic patients. The 17 % risk reduction in vascular events in diabetic patients appears less than the 22 % in non-diabetic patients, but not significantly so. Because the baseline risk is higher in the diabetic cohort the absolute benefit of treatment with aspirin/antiplatelet agents is similar in non-diabetic (36 vascular events avoided per 1000 patients) and diabetic (38 events avoided per 1000 patients) patients. Controversy exists, however, regarding the benefits of aspirin administered in the acute phase of myocardial infarction. This is mainly based on the observation that in the subgroup of 1287 diabetic subjects randomized to 160 mg aspirin daily or placebo in the Second International Study of Infarct Survival (ISIS-2), aspirin treatment produced no reduction in mortality rate.[44] It has been argued that, due to increased turnover of platelets, diabetic patients may require larger doses of aspirin to suppress the synthesis of thromboxane A_2,[45] 300 mg aspirin daily may be preferable to the 75–100 mg daily used in non-diabetic patients but this remains an area for further research. A strong case can however, be put that aspirin reduces events in diabetic patients at high cardiovascular risk such as post myocardial infarction patients.[46,47]

There are caveats to this. The Co-operative New Scandinavian Enalapril Study II (CONSENSUS II) found evidence of an aspirin – enalapril interaction such that subjects randomized to both these drugs did worse than those randomized to aspirin alone.[48] In the Studies Of Left Ventricular Dysfunction (SOLVD), enalapril did not improve the prognosis of subjects taking aspirin.[49] This has led to the notion that aspirin may not produce benefits in heart failure or that aspirin interacts with angiotensin converting enzyme inhibitors (ACEIs).[50] In addition taking aspirin is not without risks. There is a dose-dependent increase in upper gastrointestinal haemorrhage as the dose of aspirin is increased from 75 mg day^{-1} to 300 mg day^{-1}.[51] This risk is not attenuated by using enteric coated or buffered aspirin[52] and we know from randomized trials that age and cardiovascular disease are major predictors of upper gastrointestinal complications.[53] It may be possible to avoid some of this toxicity by eradicating *Helicobacter pylori*.[54] Finally, by inhibiting synthesis of renal prostaglandins, low dose aspirin doubles the risk of hospitalization for acute renal failure.[55]

Aspirin: the Verdict

The balance of evidence favours the use of aspirin in diabetic patients both acutely and as secondary prevention of myocardial infarction. The optimal dose of aspirin is unclear but may be higher than in non-diabetic individuals. There may be an unfavourable interaction with angiotensin converting enzyme inhibitors or in the presence of heart failure. When aspirin is given to older subjects, consideration should be given to *Helicobacter*

pylori eradication or co-administering a cytoprotective agent to prevent upper gastrointestinal complications.

Lipid Lowering with Statins

While there have been no studies exclusively in diabetic patients, there is convincing evidence from subgroup analyses of the major trials that cholesterol lowering therapy is beneficial in diabetic patients. The Scandinavian Simvastatin Survival Study (4S) included 204 paients with diabetes.[56] All subjects in this study had evidence of coronary disease either as angina or distant (> 6 months) myocardial infarction, and all had a total cholesterol of between 5.5 and 8.0 mmol l^{-1} (mean 6.75 mmol l^{-1}) and triglycerides < 2.5 mmol l^{-1} (mean 1.5 mmol l^{-1}). Subgroup analyses of these patients have suggested that simvastatin reduced major cardiovascular events to a greater degree in diabetic patients than non-diabetic (risk reduction 55 % vs 32 %).[57,58] The reduction in total mortality was also greater in the diabetic patients, although this was not statistically significant (43 % vs 28 %). Interestingly, the effect of simvastatin was independent of concomitant therapy with aspirin or beta blockers, suggesting that the effect was being produced by a different mechanism. The benefits of lipid lowering were similar across all four quartiles of cholesterol at entry to the study.[59] The Cholesterol And Recurrent Events (CARE) trial included 586 patients with diabetes.[60] The entry criteria for this trial were a myocardial infarction more than 3 months but less than 20 months prior to randomization (mean 10 months), a total cholesterol < 6.2 mmol l^{-1} (mean 5.4 mmol l^{-1}) and an LDL cholesterol between 3.0 and 4.5 mmol l^{-1} (mean 3.6 mmol l^{-1}). The risk reduction with pravastatin was 23 % for the non-diabetic population of this study and 25 % for the diabetic subgroup, a similar but less dramatic trend to that seen in the 4S study. In addition, a further analysis of the CARE study showed that subjects with a fasting blood glucose level at entry of greater than 6.7 mmol l^{-1} had twice the incidence of cardiovascular endpoints but similar risk reduction with pravastatin as subjects with fasting glucose < 6.7 mmol l^{-1} (risk reduction 26 % vs 23 %).[61] Very recently preliminary results from the LIPID study[62] have been presented.[63] This study randomized 9009 men and women all of who had experienced a cardiac event (myocardial infarction or unstable angina) and moderate total cholesterol levels (4–7 mmol 1^{-1}) to pravastatin or placebo. Over a 6-year period there was a 24 % reduction in coronary death ($p < 0.0005$) equivalent to 19 deaths per 1000 patients. A subgroup analysis of patients with diabetes in the LIPID study is awaited.

The benefits to be gained from secondary prevention in diabetic subjects thus appear very substantial. Whether the small reduction in cholesterol produced by diet alone is effective is unknown but it seems a reasonable strategy to augment lipid lowering drugs with diet.[64]

Lipid Lowering with Statins: the Verdict

There is compelling evidence that lipid lowering therapy post myocardial infarction would produce substantial benefits in diabetic patients. These drugs should be prescribed to diabetic patients who have suffered myocardial infarction who have a total cholesterol > 4 mmol l^{-1}.

ACE Inhibitors

Trials of ACEIs in myocardial infarction can be split into two broad groups: those that started therapy during or shortly after myocardial infarction, usually with a 4–6 week follow-up (acute trials) and those that started therapy after myocardial infarction in subjects with evidence of clinical heart failure or reduced systolic function (chronic trials). A meta-analysis of 15 acute trials encompassing 100 963 patients has shown that ACEIs reduced mortality by 6 %.[65] Contributions to this analysis come from the CONSENSUS II study[66] that gave intravenous enalapril within 24 h of myocardial infarction and described an 11 % *increase* in mortality in the enalapril group; the Fourth International Study of Infarct Survival (ISIS-4)[65] that found a 7 % *reduction* in mortality when captopril was given orally and the Gruppo Italiano per lo Studio della sopravvivenza nell-Infarto miocardico (GISSI-3) study[67] that gave lisinopril and found a 12 % *reduction* in mortality. The GISSI-3 study excluded subjects with hypotension (systolic blood pressure ≤ 100 mmHg) and subjects with severe heart failure. Subgroup analysis of GISSI-3 suggested that lisinopril reduced 6 week mortality in both Type 1 and Type 2 diabetic patients by 44 % and 27 %, respectively.[68] The disparate results of CONSENSUS II versus ISIS-4 and GISSI-3 have produced considerable debate as to whether ACEIs should be given acutely (within 24 h) in myocardial infarction.[69–72] Since diabetic patients derived more benefit from lisinopril in GISSI-3, a strong case can be made for giving ACEIs to diabetic patients who fit the GISSI-3 entry criteria.

Chronic trials, which started ACEIs a few days after myocardial infarction in subjects with left ventricular dysfunction, reduced mortality by 22 %.[73] This figure is based on the overall results of the Survival and Ventricular Enlargement Trial (SAVE),[74] the Acute Infarction Ramapril Efficacy (AIRE) study[75] (which entered subjects based on clinical heart failure) and the Trandolapril Cardiac Evaluation (TRACE) study[76] which included 22 %, 12 %, and 13 % diabetic patients, respectively. As diabetic patients were reasonably well represented, it is reasonable to generalize the results to diabetic subjects, although no specific analyses of the diabetes subgroups are available to date. A helpful piece of evidence comes from subgroup analyses of the Studies of Left Ventricular Dysfunction (SOLVD) trials.[77] These found that ACE inhibitors reduced mortality in diabetic patients to a similar degree as in non-diabetic patients. In the SOLVD treatment study, 70 % of diabetic and 64 % of non-

diabetic subjects had suffered a previous myocardial infarction, these figures being 79 % and 80 % in the SOLVD prevention study. There is thus reasonable evidence to the support the use of ACE inhibitors in diabetic patients who have suffered a myocardial infarction and who either have congestive heart failure or who have systolic dysfunction, defined as a left ventricular ejection fraction of less than 40 %.

Angiotensin Converting Enzyme Inhibitors: the Verdict

There is reasonably good evidence that ACEIs will be beneficial when given to diabetic patients with reduced systolic function or who have had clinical heart failure following a myocardial infarction. There are also data to support the use of oral ACEIs in diabetic subjects who fit the entry criteria of the GISSI-3 study which excluded patients with systolic hypotension or severe heart failure.

Combinations of Therapies

One argument often heard at scientific meetings is that the benefits derived from each class of treatment are not independent of each other and that the individual benefits cannot be additive. There are no studies which test this hypothesis in a factorial fashion. However, there are data to answer individual combinations of therapies. Subgroup analyses of data from the 4S study show that lipid lowering with statins produces benefits which appear to be independent of those produced by beta blockers of aspirin.[57] This might suggest that the effects of statins and these drugs are additive. Similarly, the CARE study[60] published a subgroup analysis which split the population into those with an ejection fraction below 40 % and those above. Since those with a low ejection fraction are very likely to have been prescribed ACEIs whereas those with normal systolic function are less likely, this study provides some evidence on the interaction between treatments with ACEIs and statins, specifically pravastatin. In fact, the benefits of lipid lowering were independent of ejection fraction, suggesting that the beneficial effects of statins are additive to ACEIs. Using a similar argument, there were additional benefits of beta-blockade in subjects randomized to receive captopril in the SAVE study, so these treatments seem additive.[39] As mentioned previously, the one combination of treatments that does not appear additive are aspirin and ACEIs.[48]

Combination Treatments: the Verdict

There are reasonable data to suggest that combination therapies may produce additive benefits. The one exception may be aspirin and ACEIs.

Other Treatments

Calcium Channel Antagonists

Although there are no data in diabetic subjects, calcium channel blockers should be avoided during and after myocardial infarction as meta-analyses suggest they are associated with unfavourable outcomes, the odds ratio for mortality being marginally increased at 1.04.[16] If a calcium channel antagonist is used, verapamil would appear to be the least likely to do harm.[72,78] Indeed, verapamil has recently received a licence for the secondary prevention of myocardial infarction in patients without heart failure where beta blockers are inappropriate. Amlodipine appears safe in subjects with severe chronic heart failure secondary to ischaemic heart disease.[79]

Antiarrhythmic Drugs

Class I antiarrhythmic drugs should not be given routinely.[16,73] Where an antiarrhythmic is indicated, beta blockers and amiodarone appear to offer the best risk/benefit profile.[16,73] A recent large study demonstrated that digoxin is safe in heart failure, most of which was secondary to myocardial infarction or ischaemic heart disease.[80]

Anticoagulants

There is evidence to suggest that diabetic patients get less benefit than non-diabetic patients from long-term anticoagulation after myocardial infarction.[81] The efficacy of anticoagulation appeared less than that of aspirin in the APRICOT study,[82] and anticoagulation was associated with more bleeding and strokes in the AFTER study.[83] Finally, the recently published Coumadin Aspirin Reinfarction Study (CARS)[84] showed that low, fixed-dose warfarin combined with aspirin (80 mg) in patients who had a myocardial infarction did not provide clinical benefit beyond that achieved with aspirin (160 mg) monotherapy. In this study 1674 of the 7123 subjects had known diabetes and subgroup analyses of these subjects confirmed that they were no different from the rest of the population. Because of these data, anticoagulation cannot at present be recommended for all diabetic patients post MI. Anticoagulants should be restricted to the specific subgroups of patients who may benefit from their use (i.e. those with mural thrombus).

Insulin

This is addressed by Professor John Yudkin in a separate review on pages 276–281.

Other Treatments: the Verdict

At present, there are no other treatments indicated in all diabetic patients post myocardial infarction.

Delivering Benefits to Patients

Evidence from the Action on Secondary Prevention through Intervention to Reduce Events (ASPIRE) study[27]

suggests that of the patients who had suffered a myocardial infarction, only 38 % of patients were receiving a beta blocker, 17 % an ACE inhibitor, 10 % a lipid lowering drug and 75 % aspirin. We have looked at data from the DARTS/MEMO collaboration which is a research database of all diabetic patients in Tayside, Scotland (population 390 000, diabetic population 7596; prevalence 1.94 %, sensitivity 95 %, positive predictive value 96 %) and records all drugs encashed at community pharmacies.[85,86] During the same period as ASPIRE, we found that 208 diabetic patients were admitted to Tayside hospitals with a first myocardial infarction. Of the patients that survived 3 months, 25 % were taking a beta-blocker, 68 % were taking aspirin and 25 % were taking ACE inhibitors and, despite cholesterol being measured in 21 % of subjects, only 2 % were discharged taking lipid lowering therapy (unpublished data: Source DARTS/MEMO database). These data describe patterns of care prior to the publication of the 4S study. We subsequently carried out an audit of prescribing of lipid lowering therapy before and after publication of the 4S study which showed that lipid lowering therapy did increase post 4S.[87] However, it is clear that we must try harder to deliver the significant benefits of secondary prevention therapy to diabetic patients who have suffered a myocardial infarction.

Conclusions

Diabetic patients appear to benefit from drug treatment (beta blockade, aspirin, lipid lowering and in selected subjects ACEIs) post myocardial infarction as much as, or more than, non-diabetic patients. The challenge we face is to deliver these benefits into routine clinical care.

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